REMARKS:

Original claims 1-10 are in the case and presented for reconsideration. Although no changes have been made to the claims, they have been reproduced in this amendment for the Examiner's convenience.

Claims 1-10 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Motola et al. US 5024997 (Motola) in view of EP 0 490 193 (EP), machine translation, and further in view of Small et al., Pharmacokinetic and Taste Evaluation of Ibuprofen (Motrin R) 800mg Tablets in Extemporaneous Solution, Journal of Reumatology 1988 Feb; 15(2): 345-7 (Small).

The object of the claimed invention of the subject patent application is stable palatable syrup containing S(+)-ibuprofen and method of its preparation. The syrup of the present invention according to Claim 1 contains S(+)-ibuprofen, hydroxypropyl beta-cyclodextrin, at least one sweetener, water and optionally essential oils in defined amounts. A method of preparation of such a syrup is characterized in that crystalline S(+)-ibuprofen is dissolved at a temperature within the range from 15 to 50° C, which is lower than its melting point, in a hydroxypropyl beta-cyclodextrin aqueous solution. The method described and claimed in the present application successfully solves the problem of obtaining a pharmaceutical preparation with masked unpleasant taste of S(+)-ibuprofen, not manifesting segregation of S(+)-ibuprofen from the solution during long term storage, without applying more complex methods of preparation.

The cited document EP relates to inclusion complexes of S(+)-ibuprofen and beta-cyclodextrins in solid form, prepared by phase-transformation technique at a

temperature above the melting point of S(+)-ibuprofen (see p. 4, l. 4-8), showing enhanced solubility and bioavailability of S(+)-ibuprofen.

The subject-matter of Claim 1 of the present application clearly differs from that of EP essentially, in more aspects. EP teaches a solid complex of S(+)-ibuprofen with cyclodextrin, prepared by phase-transformation technique, and its optional use for the preparation of a syrup. During the phase-transformation process in EP, S(+)-ibuprofen is melted in an aqueous suspension of a suitable cyclodextrin as a host molecule and after exceeding its melting point a solid crystalline complex is formed. The solid crystalline complex is dried at 60° C, i.e. at a temperature exceeding the melting point of S(+)-ibuprofen, that means that a new physical form is formed. The present application teaches a simple mixture of S(+)-ibuprofen with hydroxypropyl beta-cyclodextrin in a solution. It is well known that in a solution the stoichiometry of the complexes as well as their association constants are entirely different from the properties of the inclusion complexes in the solid phase, thereby modifying thermodynamic parameters of the resulting complexes.

Moreover, the use of the above mentioned solid crystalline complex for the preparation of the syrup containing S(+)-ibuprofen is described only in Example 10 of EP. The cyclodextrin derivative used in this example, i.e. 2,6-di-O-methyl-beta-cyclodextrin, differs from the derivative used in the present application. As physical and chemical characteristics of inclusion complexes are significantly dependent on the type of derivative modifying the native cyclodextrine, there is no evidence that a syrup according to EP could be prepared using different cyclodextrin derivative. Hydroxypropyl beta-cyclodextrin, the cyclodextrin derivative used in the present application, is mentioned only in Claims 11 and

18 of EP as one of the cyclodextrin derivatives possibly suitable for the preparation of S(+)-ibuprofen-containing solid crystalline complex. Its use for the preparation of syrup is not disclosed or suggested anywhere in EP. The person of ordinary skill in the art would therefore have no reason at all to believe that the teaching of EP can be used to reach the claimed invention, recalling that even the KSR case (*KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385 April 30, 2007) and the corresponding guidelines of MPEP 2141, require some credible reasoning for making the combination being applied against the claims.

The weight ratio of S(+)-ibuprofen to the cyclodextrin derivative in the syrup of Example 10 of EP is 1:6.47. This ratio cannot be used for the preparation of the syrup of the present invention, i.e. using the S(+)-ibuprofen solution instead of the solid crystalline complex of S(+)-ibuprofen and cyclodextrin. Long-term stability and masking of the unpleasant taste can be obtained in the liquid pharmaceutical preparations containing the non-complexed S(+)-ibuprofen only at the weight ratio of S(+)-ibuprofen and cyclodextrin of from 1:10 to 1:18. At lower weight ratios the S(+)-ibuprofen starts to segregate from the solution and the taste-masking is incomplete.

According to EP the complex of S(+)-ibuprofen and cyclodextrin derivative is being prepared at the temperature of 60° C and dried, yielding a solid substance composed of both components, which is subsequently dissolved for the preparation of the syrup. In the present application the S(+)-ibuprofen is dissolved in aqueous solution of hydroxypropyl beta-cyclodextrin at a temperature lower than the melting point of S(+)-ibuprofen, i.e. at a temperature within the range from 15 to 50° C.

The pharmaceutical preparation claimed in the present application differs from the pharmaceutical preparations of EP in the following aspects:

- use of solutions of S(+)-ibuprofen and hydroxypropyl beta-cyclodextrin instead of the preparation of a solid complex of S(+)-ibuprofen and a cyclodextrin derivative;

- the cyclodextrin derivative used for the preparation of the syrup;

- the weight ratio of S(+)-ibuprofen to hydroxypropyl beta-cyclodextrin, which substantially differs from that of S(+)-ibuprofen to 2,6-di-O-methyl beta-cyclodextrin in the complex used for the preparation of the syrup of EP; and

- the processing temperature not exceeding 50° C instead of the processing temperature exceeding the melting point of S(+)-ibuprofen, see p. 4, l. 7-8 of EP (in examples, only the processing temperature 60°C is disclosed), taught for the preparation of the complex of EP.

Accordingly the Applicants strongly believe that it clearly follows from the above arguments that the subject-matter of the present invention is not obvious to a person of ordinary skilled in the art and that the claimed invention is therefore unobvious over the cited combination of prior art that relies on EP 0 490 193.

Motola teaches the preparation of syrup containing racemic ibuprofen, in which the ibuprofen is dissolved in aqueous solution of hydroxypropyl beta-cyclodextrin at 50°C; in Example 5 of Motola the solution of racemic ibuprofen and cyclodextrin derivative is added to further components even at the temperature of 60°C. When S(+)-ibuprofen was used under the same conditions, there occurred (in the course of dissolution and stirring) its melting under the formation of a suspension which was in the long-term unstable,

physically unstable and unsuitable for pharmaceutical preparations.

S(+)-ibuprofen possesses different physical properties compared to the racemic form of ibuprofen. It shows different behaviour when being dissolved in common solvents, has a substantially lower melting point (50 to 54° C) compared to the racemate (75 to 78° C) and under neutral and basic conditions the racemization of S(+)-ibuprofen occurs. For these reasons the processes used for the racemic ibuprofen are not directly transferable to the preparation of pharmaceuticals containing S(+)-ibuprofen. The compositions and conditions which are suitable for the preparation of stable pharmaceutical preparations based on racemic ibuprofen do not provide long-term stable products in case of S(+)-ibuprofen but only products in which a micro-emulsion of S(+)-ibuprofen is formed, which is sticky and hardly removable especially at an industrial scale. This sticky layer is considerably disadvantageous especially for the production of syrup at an industrial scale. The inventors of the present invention have found that by working-up the mixture at lower temperature such undesirable effects can be avoided. Therefore in the present application the S(+)-ibuprofen is dissolved in the temperature range from 15 to at the most 50° C, preferably from 40 to 45° C, in which the undesirable effects do not occur. Treatable and long-term stable product is obtainable only by working in the temperature range not exceeding the melting point of S(+)-ibuprofen.

The present invention differs from the teaching of Motola in that S(+)-ibuprofen is used instead of racemic ibuprofen and in that it is dissolved at a temperature not exceeding its melting point, so that the undesirable effects are avoided.

The use of S(+)-ibuprofen in the mixture of Motola is not obvious if combined with, or from EP, because EP teaches the preparation of a solid complex of S(+)-ibuprofen and cyclodextrin by phase-transformation technique and subsequent drying of the formed solid

product at 60° C. EP does not propose or suggest the use of a mixture of S(+)-ibuprofen and a cyclodextrin derivative in a solution and would not lead a person skilled in the art to use S(+)-ibuprofen in the solution of EP.

The aim of the Small study was an evaluation of pharmacokinetic characteristics (as Cmax, Tmax and AUC) of high strength tablets of ibuprofen (Motrin R) after dissolution in common beverages. Motrin is a racemic mixture of both enantiomeric forms of ibuprofen. The taste evaluation of beverages with dissolved drug was influenced by taste preferences of evaluative subjects who hated or liked them. No artificial flavors of essential oils were assessed; in fact only taste acceptability of known beverages after addition of strong ibuprofen tablets was appreciated. No data was collected following S(+)-ibuprofen administration.

In comparison with the Small's study, from two to four orders of magnitude lower amounts of S(+)-ibuprofen (furthermore regarded as two fold more efficient as racemate) is considered for the syrup according to the present application. The syrup can contain an optional amount of essential oils for taste correction. The essential oils to be used include orange, lemon, lemongrass or peppermint essential oil. Preservatives, coloring and flavoring agents can be added if desired, as it will be understood by those skilled in the art. The presence of essential oil in the claimed syrup is mentioned only for describing its complete composition and it is not regarded as a special finding.

Therefore the determination of the most appropriate beverage (orange juice) for the administration of rather large tablets of racemic ibuprofen after its dissolution does not seem to be relevant for the present application.

The present solution is thus not obvious for a person skilled in the art from the combination of the cited documents. Therefore the Applicants believe that the independent Claim 1, the claims dependent on Claim 1 and the claims concerning the method of preparation of the syrup, define an unobvious invention over Motola in view of EP 0 490 193 (EP), and further in view of Small.

Accordingly, the application and claims are believed to be in condition for allowance, and favorable action is respectfully requested.

If any issues remain, the Examiner is respectfully invited to contact the undersigned at the number below, to advance the application to allowance.

Respectfully submitted,
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